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NEPHROLOGY FORUM

Diagnostic approach to hypercalciuria

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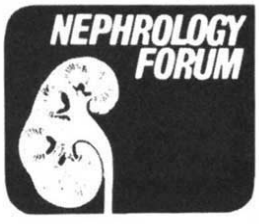
The *Nephrology Forum* is designed to relate the principles of basic science to clinical problems in nephrology.



Case Presentation

A 40-year-old woman was admitted to the metabolic ward of St. Vincent's Hospital in Dublin. Two years previously, she had been admitted to the genitourinary ward because of left renal colic. At that time, an i.v. urogram showed bilateral spotty nephrocalcinosis in kidneys of normal size, and a solitary renal cyst was visible on the right side. Laboratory findings disclosed the following: hematocrit, 47%, blood urea nitrogen (BUN), 10 mg/100 ml; serum sodium, 141 mEq; serum potassium, 4.4 mEq; serum chloride, 104 mEq; serum bicarbonate, 26 mEq/liter; serum uric acid, 3.8 mg; total calcium concentration from a single sample of serum, 10.7 mg (normal, 9.0 to 10.6 mg, 95% limits) and ionized serum calcium, 5.5 mg/100 ml (normal, 4.1 to 5.3 mg/100 ml, 95% limits); urine calcium, 262 mg/24 hr (normal < 250 mg/24 hr); the urine sediment was unremarkable, and a culture of the urine was sterile.

One year later, the patient entered the outpatient clinic with an episode of right renal colic. On this occasion, total serum calcium concentration was 10.3 mg and ionized serum calcium was 5.5 mg/100 ml; a simultaneous parathyroid hormone (iPTH) level was 0.18 ng/ml as measured by radioimmunoassay using the Slatopolsky carboxy-terminal specific antiserum (normal range, 0.0 to 0.33 ng/ml). The findings of a second i.v. urogram indicated no change in kidney status; there was no evidence of pelvi-ureteric dilatation. The patient was admitted subsequently to the metabolic ward for investigation of hypercalciuria, nephrocalcinosis, and marginal hypercalcemia, although iPTH level was apparently normal.

On admission the patient had no history of excessive ingestion of milk, oral alkali preparations, or vitamin supplements. Her mother and brother each had had one episode of renal colic in the past. Physical examination was unremarkable with blood pressure of 110/70 mm Hg. Laboratory findings revealed the following: hematocrit, 43%; white blood cell count, 6700 mm^3; sedimentation rate, 1 mm/hr; urine protein was absent; EKG was normal; chest radiogram showed healed tuberculous foci; radiograms of the hands were normal; BUN, 12 mg/100 ml; serum sodium, 142 mEq; serum potassium, 4 mEq; serum chloride, 107 mEq; serum bicarbonate, 23.5 mEq/liter; total protein, 7.2 g; serum albumin, 4.6 g/100 ml; alkaline phosphatase, 7.4 King-Armstrong U; serum creatinine, 0.9 mg/100 ml. For 4 days, a fixed diet that contained 500 mg of calcium and 1 g of phosphorus was given to the patient; laboratory values for serum taken on the mornings of days 3 and 4 were; total calcium, 9.9 and 10.0 mg; ionized calcium, 5.2 and 5.1 mg; phosphate was 2.7 mg/100 ml on both mornings (normal, 2.6 to 4.2 mg/100 ml). The following additional laboratory values were obtained on mornings 3 and 4; urinary calcium, 323 and 289 mg/24 hr; percent of tubular reabsorption of phosphate, 74.5 and 76.8% (normal, 83 to 87%). Serum iPTH levels were 0.57, 0.35, and 0.55 ng/ml. The serum level of 25-hydroxy vitamin D was 6.9 ng/ml (normal, 11.8 ± 4.0 ng/ml).

In spite of five normal values for total serum calcium obtained in the fasting state (mean, 10 mg/100 ml), it was decided to refer the patient for surgical exploration of the neck because her mean ionized serum calcium concentration of 5.4 mg/100 ml was at the upper 95% limit of normal, and because three of four iPTH values were elevated. Serum taken on the morning of parathyroid surgery showed total serum calcium concentration to be 10.5 mg and ionized serum calcium, 5.7 mg/100 ml. The 24-hour urinary calcium excretion was 349 mg. The surgical procedure revealed an enlarged parathyroid gland. The gland, weighing 360 mg, was removed; the tissue was adenomatous on histologic examination. Two other parathyroid glands were biopsied and proved to be normal. The patient's postoperative course was uneventful. Review after 5 months revealed a total serum calcium concentration of 8.8 mg, an ionized serum calcium concentration of 5 mg/100 ml, a urinary calcium excretion of 184 mg/day, and a serum iPTH level of 0.14 ng/ml.

Discussion

DR. FRANCIS P. MULDOWNEY *(Research Professor of Medicine, University College, and Physician-in-Charge, Metabolism and Renal Unit, St. Vincent's Hospital, Dublin):* I believe the diagnostic

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problem of renal stone disease is best approached, not by a long and learned list of causes, but by remembering the relative frequency of the most important ones. In 1970, Yendt [1] provided a most helpful breakdown of his series of 439 patients with renal stone disease: he showed that 42% had idiopathic hypercalciuria, 11% had primary hyperparathyroidism, 8% had urinary infection, 5% had uric acid stone, and 2% had cystinuria; no cause was found in 24%. This is a convenient list to remember at the bedside and puts into perspective the relative importance of, for example, infection/obstruction, which is a minor cause, and idiopathic hypercalciuria, which is a major cause of renal stone disease. One may note that more sophisticated renal tubular disease, such as classical renal tubular acidosis or medullary sponge kidney, scarcely deserve mention. Nevertheless, a systematic approach to the diagnosis in each patient must attempt to be reasonably comprehensive as well as crudely practical; one must know each horse in the race as well as the betting odds. Idiopathic hypercalciuria may be the "favorite"; but it may just occasionally take second place to an outsider such as milk-alkali syndrome!

With this in mind, Figure 1 sets out a sequence of diagnostic steps using certain key techniques in the order best calculated to give weight to the major causes, while allowing necessary consideration to the minor ones. The first question is whether hypercalciuria is present. If not, we move into a minor pathway to consider causes such as infection/obstruction, urate stone, or cystinuria. Patients with either of the latter two conditions frequently have a familial history that is helpful, and laboratory data such as serum uric acid concentration and results of urinary amino acid chromatography enable one to make the diagnosis. Infection, obstruction, urate stone, or cystinuria are causal factors in some 15 to 20% of all patients with renal stone disease [1].

The presence of hypercalciuria may be documented in a number of ways. The standard indicator is 24-hour urinary calcium excretion—upper limits of normal are 300 mg in the male and 250 mg in the female [2]. The patient under discussion today, a female, had a 24-hour urinary calcium excretion in excess of 250 mg on 2 successive days while receiving a diet that contained 500 mg of calcium. An additional index of hypercalciuria is the fasting morning "spot" urine calcium concentration as it relates to filtered calcium load (see Table 1). This measurement has the great advantage of avoiding the cumbersome collection of total 24-hour volume, which is prone to collection errors and the consequent variability of results. For instance, a fasting urinary calcium to creatinine concentration ratio or a urinary calcium per 100 ml of glomerular filtrate that exceeds 0.11 is likely to represent hypercalciuria. The "spot" urine calcium to creatinine concentration ratio provides a useful screening test for the busy nephrologist and may be repeated as often as desired.

If hypercalciuria is present as in our patient today, the next question is whether the *serum* calcium concentration is elevated. If the serum calcium concentration appears to be normal, and if no

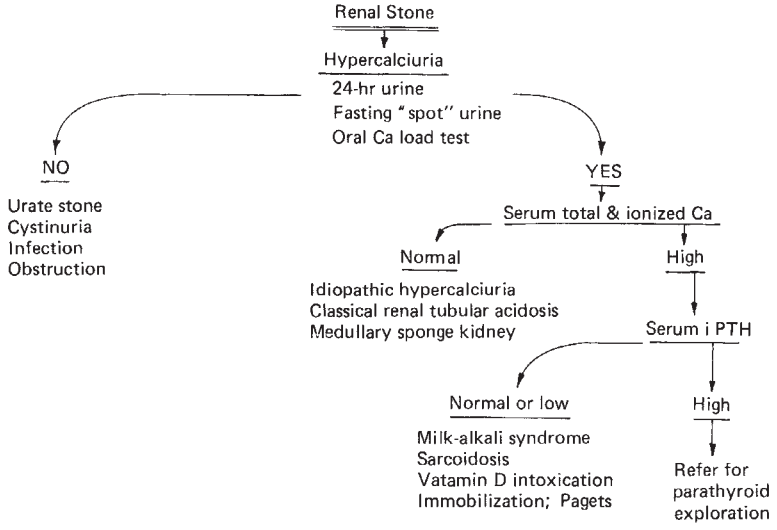

Fig. 1. *Suggested scheme of approach to diagnosis in renal stone disease based on presence or absence of hypercalciuria, hypercalcemia, and serum parathyroid hormone* (iPTH) *elevation.*

Table 1. Urinary and serum calcium (Ca) in the fasting state and following oral loading with Ca, 30 *mg/kg* of body weight.

		Control $n = 9$[a]	Idiopathic hypercalciuria $n = 18$	Control vs idiopathic hypercalciuria
Creatinine (Cr) clearance, *ml/min*		106 ± 16	103 ± 17	NS
Total serum Ca, *mg/100 ml*	Fasting	9.25 ± 0.41	9.35 ± 0.36	NS
	Post-load[b]	10.0 ± 0.52	10.24 ± 0.48	NS
		< 0.02	< .001	
Ionized serum Ca, *mg/100 ml*	Fasting	5.02 ± 0.29	4.86 ± 0.21	NS
	Post-load	5.24 ± 0.24	5.16 ± 0.31	NS
		< 0.2	< .005	
Urine Ca, *mg/100 ml GF*[c]	Fasting	0.07 ± 0.051	0.149 ± 0.078	< 0.01
	Post-load	0.241 ± 0.069	0.355 ± 0.084	< 0.005
		< .001	< .001	
Urine Ca/Cr ratio	Fasting	0.068 ± 0.044	0.149 ± 0.076	< 0.001
	Post-load	0.233 ± 0.077	0.354 ± 0.069	< 0.001
		< .001	< .001	
Urine Ca as percent filtered ionized Ca	Fasting	1.87 ± 0.87	3.23 ± 1.48	< 0.05
	Post-load	4.45 ± 1.27	7.04 ± 1.69	< 0.001
		< .01	< .001	

[a] *n* denotes number of patients
[b] Post-load data refer to the collection period 3 to 4 hours following ingestion of the calcium.
[c] GF denotes glomerular filtrate

other demonstrable cause is apparent, the diagnosis of idiopathic hypercalciuria can be made with some assurance. If the serum calcium concentration is elevated, however, the alternate pathway of investigation should be taken using iPTH level as a main determinant of management. Note that this pathway ends either with surgical neck exploration for a parathyroid adenoma, or with evaluation directed toward nonparathyroid causes of hypercalcemia, most of which are reversible, such as milk-alkali syndrome. Before proceeding along either route, one must be reasonably certain that hypercalcemia does or does not exist. If the wrong route is taken because of incorrect or inadequate laboratory evaluation, the patient may receive inappropriate therapy. There are two classic examples of this problem: administration of thiazide therapy for supposed idiopathic hypercalciuria that is really undocumented primary hyperparathyroidism; and fruitless neck exploration and biopsy in a patient with normal parathyroid glands. I should mention one further unfortunate consequence of the wrong decision at this critical juncture. The definition and subsequent investigation and classification of patients who are predisposed to the formation of renal stones may be unintentionally obscured, and incorrect assumptions may be made concerning etiology and pathophysiology for each subgroup, unless clear lines of distinction and definition are seen and agreed to by all workers in the field. The techniques that are available today were not available 10, 15, or 30 years ago when many of the standard investigations were made. [3, 4, 5]. At that time, conclusions were based on values for total serum calcium or perhaps ultrafilterable calcium concentration only. It is now possible to measure the ionized fraction of the calcium concentration by ion-specific electrodes and the iPTH level by a sensitive radioimmunoassay; thus, the onus is on us to assess the value of these data in the same critical fashion as was done for the less revealing data relied on in the past.

Idiopathic hypercalciuria accounts for 42% of all cases of renal stone disease [1]. Unfortunately, it resembles the next most common cause, primary hyperparathyroidism, in many ways. The critical distinguishing feature between the two disorders is the presence or absence of hypercalcemia: Both frequently show hypercalciuria; both may show hypophosphatemia with lowered tubular phosphate reabsorption; and to make difficulty doubly defiant, Coe et al [6] have demonstrated that both may show elevated immunoreactive serum iPTH levels. Our immediate problem in this patient, therefore, is one familiar to all nephrologists, that of differentiating between idiopathic hypercalciuria and primary hyperparathyroidism. Since such differentiation is achieved classically by the presence or absence of hypercalcemia, we must devote some time to that particular point.

Florid hypercalcemia is, of course, identified easily—that is, a serum calcium concentration above 11 mg/100 ml, which corresponds to the 99% con-

fidence limit (+3 SD) of the normal range. Our control studies show that serum calcium values between 10.9 and 10.6 mg/100 ml correspond to the 99 and 95% confidence limits, respectively, and thus would be expected to occur in 2.5% of the normal population; values between 10.5 and 10.2 mg/100 ml (+1 SD) would be expected in about one-sixth of the population. "Hypercalcemia" or "normocalcemia" are, therefore, inappropriately absolutist terms that should be defined rather by the levels of confidence or degrees of doubt! We prefer not to use the term "normocalcemia" and consider all values above 10 mg and below 11 mg/100 ml to be indicative of marginal hypercalcemia. These values immediately suggest to us the following tactics: (1) repeated, careful laboratory examination of samples taken in the fasting state and with minimal venous stasis and (2) further corroboration by measuring the ionized serum calcium concentration with an ion-specific, flow-through electrode. In the patient discussed today, the grand mean value for total calcium concentration was 10.0 mg/100 ml—less than 1 SD above the average normal level—whereas the ionized serum calcium concentration was more clearly elevated at 5.3 mg/100 ml, or 2 SD above the average normal value. This comparison reflects accurately the relative values of the two techniques in our experience [7]. In short, a marginal finding for total serum calcium concentration in primary hyperparathyroidism appears to be more easily defined, and with greater statistical confidence, by measuring the ionized fraction of the serum calcium concentration.

If significant hypercalcemia can be confirmed, the next question is whether it is of parathyroid or nonparathyroid origin. The logical sequence leads to measurement of serum iPTH level. We have used Slatopolsky's excellent antiserum for some years, and the results in the important group of patients who have marginal primary hyperparathyroidism are illustrated in Figure 2. In 1975 and 1976, we originally defined the limits above which neck exploration should be advised. At that time, we felt that an ionized serum calcium concentration above 5.6 mg/100 ml, i.e., +3 SD, with a serum iPTH level above the upper limit of normal, 0.33 ng/ml, should be the proper conservative guidelines, which would avoid inappropriate surgery in patients who did not have primary hyperparathyroidism [7]. With accumulating experience, we have now lowered the limit to 5.3 mg/100 ml, i.e., +2 SD, for ionized serum calcium concentration, provided that the iPTH level is elevated. Twelve patients with values for total

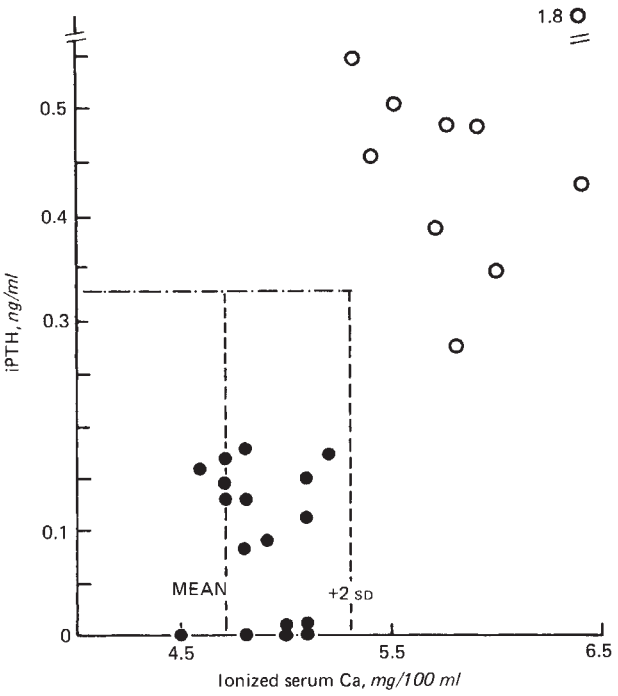

Fig. 2. *Relationship in renal stone disease of serum parathyroid hormone* (iPTH) *to ionized serum calcium* (Ca) *values in patients with marginal primary hyperparathyroidism* (open circles) *and idiopathic hypercalciuria* (closed circles). Mean +2 SD indicated for ionized Ca. Total normal range indicated for iPTH. "Marginal" refers to proven primary hyperparathyroidism with serum total Ca between 10 and 10.9 mg/100 ml.

serum calcium of 10.9 mg/100 ml or less—six, 10.4 mg/100 ml or less—and ionized serum calcium of 5.3 mg/100 ml or more have been referred for neck exploration. In ten patients, iPTH level was available, and it was elevated in nine. In each patient, the presence of primary hyperparathyroidism was confirmed at surgery: adenoma was found in ten patients, and multiple hyperplasia was found in two.

It should be noted further that seven of the patients with idiopathic hypercalciuria continue to show ionized serum calcium values at or above the +1 SD level. Although iPTH levels are normal or low in this group, one must accept the possibility that these may represent primary hyperparathyroidism of mild degree, which is undetectable by current immunoassay techniques. Thus, it is possible that all patients with idiopathic hypercalciuria reflect a spectrum of mild but currently undetectable hyperparathyroidism. We do not, however, advocate neck surgery in this group since hypercalciuria can be easily controlled by oral chlorthalidone in the majority of patients.

In the case of hypercalcemia that is not associated with hyperparathyroidism, as shown by normal

or low iPTH levels (Fig. 1), the clinical history and routine investigation should carefully exclude known causes such as milk-alkali syndrome, Paget's disease, prolonged immobilization, vitamin D intoxication, and sarcoidosis. All of these may be associated with hypercalcemia, which is often rather fleeting and mild in character. Milk-alkali syndrome represents a form of calcium-induced renal tubular alkalosis with a high tubular bicarbonate threshold [8, 9]. Vitamin D ingestion, like milk-alkali intake, may not be admitted or even realized by the patient, and measurements of serum 25-hydroxy vitamin D concentration may be necessary [10]. Both vitamin D and milk-alkali ingestion are associated with systemic alkalosis in contrast with the acidosis and hyperchloremia that may be seen in hyperparathyroidism [11]. The patient under discussion today showed a mild hyperchloremic acidosis, which was a helpful diagnostic indicator.

The mechanism of hypercalciuria in hypercalcemia is thought to be a simple increase in filtered calcium load. An exception to this general rule would be provided if glomerular filtration rate (GFR) had decreased, as commonly happens in chronic cases. Some have taken the view that primary hyperparathyroidism is also an exception because the effect of PTH-induced hypercalcemia to increase the filtered load of calcium is thought to be offset by a direct stimulating effect of the hormone on tubular reabsorption [12]. It is difficult, however, to find convincing data to support this conclusion in the clinical sphere. In the patients studied by us shown in Table 2, hypercalciuria was visible even in those patients with primary hyperparathyroidism in whom serum calcium concentration and filtered load were only minimally elevated. This finding held true both for the data derived from 24-hour urine collections and for the data derived from fasting morning urine specimens [13]. Thus, even if the filtered calcium load is elevated to a minimal degree, it is not compensated for by increased tubular calcium reabsorption despite high circulating iPTH levels. Primary hyperparathyroidism therefore remains an important cause of hypercalciuria even in patients with minimal hypercalcemia. Whether hypercalciuria in primary hyperparathyroidism at any given calcium concentration is less than in other causes of hypercalcemia may require further documentation. At this point, however, the argument becomes somewhat academic and scarcely relevant to the differential diagnosis of clinical hypercalciuria. Genuinely relevant, however, is the close resemblance of so-called "resorptive" hypercalciuria due to primary hyperparathyroidism and "renal" hypercalciuria in the sense that both clearly show increased fractional calcium excretion. Thus a renal calcium "leak" becomes yet another point of similarity between primary hyperparathyroidism and its great simulator, idiopathic hypercalciuria.

If hypercalcemia is excluded, our diagnostic scheme (Fig. 1) leads to the category of normocalcemic hypercalciuria of which idiopathic hypercalciuria is the most important member. Other causes, such as classical or distal renal tubular acidosis and medullary sponge kidney, are readily excluded by serum and urine acid-base measurements

Table 2. Urinary calcium (Ca) in relation to serum Ca concentration and parathyroid hormone (iPTH) level in primary hyperparathyroidism and in idiopathic hypercalciuria.[a]

		Urine		Serum		
		Ccr[b] *ml/min*	Ca *mg/24 hrs*	Total Ca *mg/100 ml*	Ionized Ca *mg/100 ml*	iPTH *ng/ml*
Hypercalcemic hyperparathyroidism	mean	72.9	434	12.4	6.8	0.81
	SD	23.2	210	1.5	1.2	0.22
	N[c]	11	11	11	11	11
Marginal hyperparathyroidism	mean	94.6	329	10.5	5.7	0.71
	SD	25.4	98	0.2	0.3	0.34
	N	12	14	14	14	12
Idiopathic hypercalciuria	mean	103	372	9.4	4.9	0.09
	SD	17	63	0.4	0.2	.07
	N	18	18	18	18	17
Normal			below 300 (male) below 250 (female)	9.8 ± .9	4.7 ± .6 (± 2 SD)	0.15 ± .06

[a] Urinary Ca is seen to be elevated in all, including those patients with hyperparathyroidism who have minimal elevation of serum Ca concentration (marginal hyperparathyroidism).

[b] Ccr denotes creatinine clearance

[c] n denotes number of patients.

or by careful i.v. urographic examination for caliectasis. The etiology of idiopathic hypercalciuria has been a favorite topic of argument for some years because the intestinal calcium hyperabsorption theory [5, 14, 15] has been opposed to the renal calcium "leak" theory supported by Coe et al [6]. Based on our recent measurements of fractional excretion of filtered ionized calcium, we have concluded that all patients with idiopathic hypercalciuria can be shown to have a renal calcium leak [13]. Table 1 lists urine calcium expressed in three different ways in relation to GFR or filtered calcium load. Compared with normal control patients, the group of patients with idiopathic hypercalciuria excrete a higher proportion of filtered calcium. Most patients show excessive fractional excretion even in the fasting state. Almost all patients show this characteristic in the period following oral calcium loading. We have recently confirmed this post-load tubular "leak" pattern even in those patients with hypercalciuria who have the mildest degree of calcium leak, as indicated by normal fasting urinary calcium to creatinine concentration ratios [13]. This latter group had previously been designated to be "absorptive" by Pak et al [15].

I should like to stress that we have looked carefully in our patients with idiopathic hypercalciuria at serum calcium concentration following calcium loading. The earlier data of Peacock, Knowles, and Nordin [5] had suggested a greater increment in serum calcium concentration in patients with idiopathic hypercalciuria compared with control patients. This indeed has been one of the major arguments adduced in favor of the intestinal hyperabsorption theory [14, 15]. We have not, however, found any difference in postabsorptive serum calcium concentration between our two groups; both control patients and patients with idiopathic hypercalciuria reached exactly similar concentrations of total and, in particular, of ionized serum calcium [13]. Thus, the sequence postulated by Pak et al [15]—calcium hyperabsorption causing hypercalcemia, which suppresses PTH and thereby diminishes tubular calcium reabsorption—cannot be sustained in view of the essential absence of relative post-absorptive hypercalcemia. Neither can normal or low values for serum iPTH (see Table 2) obtained 12 hours after the last meal in fasting patients with hypercalciuria be reasonably related to a theoretical post-prandial hypercalcemia. In retrospect, the patients thought to have idiopathic hypercalciuria by Peacock, Knowles, and Nordin [5] included several who initially were suspiciously hypercalcemic compared with controls and indeed overlapped the range of 10 to 10.5 mg/100 ml, which includes many of our patients with marginal primary hyperparathyroidism (see Table 2). It does not therefore seem surprising that following oral calcium loading the serum levels of such patients should show an inordinate increase, as indeed our own data in similar patients with marginal hyperparathyroidism amply confirm [13]. Once again, one may stress the importance of careful preliminary exclusion of masked primary hyperparathyroidism with marginal hypercalcemia from any apparent idiopathic hypercalciuria grouping before proceeding to make deductions concerning intestinal or renal tubular function. Of course, some degree of intestinal hyperabsorption does exist, and this has indeed been demonstrated in external balance studies [16]. Dr. John Ryan of our department (RYAN, personal communication, 1979) has confirmed such a pattern using ^{45}calcium in five of our patients with idiopathic hypercalciuria. Hyperabsorption may, however, be a compensation for renal calcium loss rather than an initiating stimulus, as was pointed out by Jackson and Doncaster in 1959 [17]. Our data are consistent with this view.

To summarize so far, our data suggest strongly that hypercalciuria in the idiopathic syndrome is due to diminished renal tubular calcium reabsorption, or a renal "leak". We therefore agree essentially with the concept supported by Coe et al [6], with the important exception that we do not confirm their postulate that such a leak gives rise to secondary hyperparathyroidism. In our experience to date, all patients with genuinely normal calcium concentration who had stone formation and hypercalciuria—that is, idiopathic hypercalciuria carefully defined—showed normal serum iPTH levels. Those of our patients with hypercalciuria who showed elevated iPTH levels also showed significantly elevated serum concentration of ionized calcium and were later shown at neck surgery to have primary hyperparathyroidism.

Indeed, one must question seriously the assumption that a mild chronic increase in urinary calcium excretion causes a decrease in ionized serum calcium concentration with a resulting increase in serum iPTH levels [6]. McCarron et al [18] have recently demonstrated that an increase in urinary calcium to 300 mg/day on a chronic basis by oral sodium loading does not result in a decrease in ionized serum calcium concentration or an increase in iPTH level. The earlier study of Coe et al [6] had demonstrated that an increase in urinary calcium concen-

tration could be induced by daily furosemide administration for 1 week. Under these circumstances, iPTH levels increased, but it is not clear that the increase in urinary calcium excretion was the responsible factor or even that hypocalcemia resulted. A decrease in extracellular fluid volume, for instance, may have been important. Rosenbaum et al [19] have shown that an increase in antidiuretic hormone excretion, such as might be expected following furosemide administration, is accompanied by increasing iPTH plasma levels. The data of McCarron et al [18] are important because they showed that an increase in urinary calcium excretion produced by sodium loading with *increased* extracellular fluid volume resulted in no change in ionized serum calcium concentration and a slight decrease in iPTH level.

The mechanism of the renal tubular "leak" of calcium in idiopathic hypercalciuria must at present remain open to speculation. Elevated serum concentrations of 1,25-dihydroxy vitamin D have been reported [20] and may represent either a primary defect or one generated by the phosphate depletion that results from the well-described defect in tubular phosphate reabsorption. Alternatively, as mentioned earlier, a spectrum of underlying primary hyperparathyroidism of varying mildness or severity may induce both renal phosphate loss and excess generation of 1,25-dihydroxy vitamin D in renal parenchyma. Whatever the ultimate defect may be, the net effect appears as hypercalciuria apparently due to diminished tubular calcium reabsorption, with intestinal hyperabsorption acting in a compensatory fashion only. In discussing this patient for the *Nephrology Forum,* it seems appropriate to rescue idiopathic hypercalciuria from its status as a plaything of the gastroenterologists and to bring it back firmly to the kidney where it surely belongs!

Questions and Answers

DR. JOHN DONOHOE (*Consultant Nephrologist, Mater Misericordiae Hospital, Dublin*): Thank you very much Dr. Muldowney for that eloquent discussion. Your stirring conclusion is dear to the heart of any nephrologist! I should like to begin the question and answer period by asking a general question. As you know, urinary calcium excretion is diminished by administration of thiazides in patients with idiopathic hypercalciuria. Coe has shown that serum iPTH levels, which are significantly higher than controls prior to thiazide therapy, return virtually to normal with thiazides [6]. He interpreted these findings to be consistent with secondary hyperparathyroidism consequent to a primary renal leak of calcium. In regard to the patient presented today, I wonder if you might have considered carrying out a therapeutic trial of thiazides to delineate further the mechanism of the hypercalciuria?

In addition, do you know of any studies that focus on "autonomy" of the parathyroid glands in idiopathic hypercalciuria? Have there been any efforts, for example, to determine by calcium infusion whether hyperparathyroidism is primary or secondary in such patients?

DR. F. P. MULDOWNEY: The difficulty about suppression tests is that not only can secondary hyperparathyroidism be suppressed, but many patients with primary hyperparathyroidism can ultimately be suppressed as well. Potts et al [21] have shown that many patients with adenomatous parathyroid tissue have decreased plasma iPTH levels following calcium infusion, and we have confirmed that finding [7]. We have shown that, both in patients with secondary hyperparathyroidism of intestinal malabsorption and in those with adenomas or primary hyperparathyroidism, a calcium infusion will suppress iPTH levels. For that reason, it has always seemed to me to be unsatisfactory to use suppressibility as an index to determine whether a given patient has primary or secondary hyperparathyroidism. The data obtained by Coe et al [6], I feel, can be interpreted as indicating primary hyperparathyroidism as easily as secondary hyperparathyroidism, although the latter was the chosen interpretation of the study. The same rationale applies to the recent data of Bordier et al [22] in which sufficient 25-hydroxy vitamin D was given orally to raise serum calcium concentration. They found that in approximately one-half of the patients the iPTH level was suppressible by that technique; in the other half it was not, but the significance of this finding is not really clear.

DR. J. T. HARRINGTON: Dr. Muldowney, I have a problem in understanding the precise reasons for hypercalciuria in patients with so-called normocalcemic hyperparathyroidism. It has been argued that patients with primary hyperparathyroidism are hypercalciuric because of the hypercalcemia and the consequent increased filtered load of calcium; the latter is thought to override the direct tubular effect of parathyroid hormone, namely, to increase distal calcium reabsorption. The patient presented today had a normal ionized serum calcium concentration at times, yet she was still hypercalciuric. How do you explain this?

DR. F. P. MULDOWNEY: This is an important point. As I mentioned earlier, we do know from micropuncture studies that the effect of PTH on the kidney is to promote the tubular reabsorption of calcium. This effect has been widely extrapolated in the clinical sphere to suggest that those patients who are hypercalcemic from hyperparathyroidism have a lower urinary calcium excretion than those who are hypercalcemic to the same degree from other causes. The data to support this hypothesis are amazingly scanty, so scanty that I cannot find any. Our population is in many ways an ideal group in which to conduct such a study because primary hyperparathyroidism is being defined in a group whose excess filtered load is very small because their degree of hypercalcemia is very minor (see Table 2); if the effect of a high PTH level in promoting tubular reabsorption were ever going to overcome the effect of a high filtered load, it should do it in this group. In fact, hypercalciuria is a feature in a significant number of patients in the group; thus, they are hypercalciuric even at a time when the increase in the filtered load is minimal. I think this indicates that even in the very marginal, minimally hypercalcemic patient with primary hyperparathyroidism, hypercalciuria is still a feature. Therefore, the general rule holds that hypercalcemia from any cause, including primary hyperparathyroidism, is associated with hypercalciuria. The only exception to that would be a patient who has a significant reduction in GFR.

DR. BRENDAN DUFFY (*Consultant Nephrologist, Regional Hosptial, Galway*): *First,* could you comment on the level of serum phosphate in your patients with idiopathic hypercalciuria? As you know, phosphate depletion produces a marked hypercalciuria. *Second,* is there any evidence of "incomplete" renal tubular acidosis in these patients, and if so, what is its relationship to PTH?

DR. F. P. MULDOWNEY: The presence of phosphate depletion in idiopathic hypercalciuria is interesting because, as I mentioned earlier, this condition resembles primary hyperparathyroidism. Indeed, phosphate depletion may be the primary defect in idiopathic hypercalciuria. As you noted, it tends to cause hypercalciuria, perhaps directly or perhaps because it promotes the metabolism of vitamin D rapidly from 25-hydroxy to 1,25-dihydroxy vitamin D. Phosphate depletion is a stimulator of the 1-hydroxylase system in the kidney. As a result, you would expect to find a high concentration of 1,25-dihydroxy vitamin D in the serum, and indeed this has been found in the syndrome of idiopathic hypercalciuria [20]. On the other hand, it may be that 1,25-dihydroxy vitamin D itself causes hypercalciuria, and this may be the reason why many of these patients have a mild compensatory gastrointestinal calcium hyperabsorption. To answer your second question, we have shown renal tubular acidosis in patients with marginal hyperparathyroidism [7], and we think this is due to the excess circulating PTH levels. In the group of patients with idiopathic hypercalciuria, we have not seen a significant systemic acidosis except with a few patients who had a rather low serum bicarbonate concentration and a slight lowering of the bicarbonate reabsorption threshold. We didn't attempt bicarbonate loading in the patient under discussion because I didn't think we stood to gain much from it.

DR. DERMOT MURNAGHAN (*Consultant Nephrologist, Regional Hospital, Cork):* Could you review your thoughts regarding your patients in whom hypercalciuria persisted postoperatively? This finding suggests that there is a primary renal calcium leak in at least those patients.

DR. F. P. MULDOWNEY: Dr. Murnaghan's point is well taken; to what extent does the hypercalciuria persist in patients thought to have primary hyperparathyroidism despite removal of the adenoma? If it persists, it might lead one to believe that the primary calcium leak was the first event that gave rise to secondary hyperparathyroidism, which ultimately became autonomous and primary. Fair enough. In our group of 15 patients, 12 patients did in fact become normocalciuric and 3 remained hypercalciuric following removal of the adenoma. Perhaps your question recalls the data of Bordier in which he demonstrated persistence of hypercalciuria in patients following removal of the adenoma. But he had loaded all of the patients with sufficient 25-hydroxy vitamin D prior to surgery to produce further hypercalcemia and undoubtedly hypercalciuria. I feel that such loading is really a gentle intoxication and I suspect that the patients in our group would have reacted with persistent hypercalciuria. Whether the hypercalciuria would have been due to the intrinsic defect or to the vitamin D intoxication is impossible to determine.

DR. DAVID POWELL *(Consultant Endocrinologist, Mater Misericordiae Hospital, Dublin):* We are concerned with the difficulty in distinguishing idiopathic hypercalciuria from mild primary hyperparathyroidism because of the substantial therapeutic implications. We anticipate a low total serum calcium concentration in patients with idiopathic hypercalciuria, but a relatively elevated total serum

calcium concentration, at least in the upper range of normal, in patients with mild hyperparathyroidism. You have shown that the mean total serum calcium concentration is low in your patients with idiopathic hypercalciuria but the ionized fraction is high. It appears that the total serum calcium concentration is not a good reflection of the ionized serum calcium concentration in patients with idiopathic hypercalciuria; there seems to be a slightly greater proportion of total serum calcium in ionized form in patients with idiopathic hypercalciuria than in control patients. I wonder if you could explain this in physicochemical terms?

DR. F. P. MULDOWNEY: We wonder how to explain it too. There is no doubt that the patients with idiopathic hypercalciuria [13] have a total serum calcium concentration—9.4 ± 0.4 mg/100 ml—that appears to be below the normal mean—9.8 ± 0.4 mg/100 ml—whereas the ionized serum calcium concentration is above it. Whether this is a PTH-induced effect or some totally unknown effect is not clear, but the phenomenon is there and it is an important one.

DR. BRIAN KEOGH *(Consultant Nephrologist, Meath Hospital, Dublin):* What are your thoughts on screening for other factors that might be involved in calicium stone formation, such as increased urinary uric acid concentration or oxalate excretion?

DR. F. P. MULDOWNEY: In screening patients we do include the serum uric acid concentration, although urinary uric acid concentration is not sought. I am aware of the theory discussed by Coe [23] that high urinary excretion of uric acid may tend to "inhibit the inhibitors" of calcium crystalization in the urine. The phenomenon appears to be true but I have not yet found the information to be meaningful in a diagnostic situation.

DR. J. T. HARRINGTON: You place a great deal of weight on the results of the ionized serum calcium determination in your evaluation of patients with idiopathic hypercalciuria. In its absence would you use parathyroid venous drainage localization studies either in primary hyperparathyroidism or in patients being re-operated?

DR. F. P. MULDOWNEY: We have used the localization studies—that is, putting a catheter into the venous drainage of the thyroid and parathyroid areas—in a few situations. The patients in whom we have used it are those in whom we have genuine doubts whether hypercalcemia is of parathyroid origin or neoplastic origin. That is, of course, a totally different situation than defining the origins of kidney stones. Fortunately, hypercalcemia induced by a PTH or PTH-like substance secreted from a tumor does not usually last long enough to produce a renal stone. I am a little worried about the venous catheterization studies because they are rather complex maneuvers in themselves. An excellent radiologist and a catheterizer are required to do them, and the procedure is rather lengthy. Surgical exploration for parathyroid adenoma would seem to be as practical. With the catheterization studies, it is not always clear what might be the gradient in the venous effluent from a normal parathyroid gland compared with a drainage of the venous effluent from, say, the thyroid. Perhaps Dr. Powell would comment on this technique.

DR. D. POWELL: In patients with cancer-induced hypercalcemia, we do not find high iPTH levels [24], though we have performed catheter studies to diagnose coincident hyperparathyroidism in a patient with cancer [25]. In patients with hyperparathyroidism, thyroid vein catheterization is a little complex, certainly, and requires special radiological skill. It is performed in the awake patient, is not painful, causes no morbidity, and is a useful pre-operative procedure for many patients with overactive parathyroid glands.

To answer the query raised, we studied parathyroid gradients in thyroid veins in patients with parathyroid disorders [26] and also in patients without any calcium disorder [27]. Comparable gradients were found in both groups, though of course absolute values were higher in those with overactive parathyroids. So the size of the gradient is not diagnostic but depends on the size of the vein catheterized, and the degree of dilution of the gland effluent. The major worth of the technique as a diagnostic tool is in patients with established hyperparathyroidism in whom bilateral thyroid vein gradients indicate four-gland hyperplasia, whereas a unilateral gradient—that is, no gradient on the other side and thus a value the same as the peripheral level—indicates a single source of secretion, an adenoma, on the side of the gradient. This is the information the surgeon needs.

DR. J. DONOHOE: Dr. Muldowney, could you comment on the present thinking regarding the importance of "inhibitors" of stone formation in the genesis and treatment of calcium stones? Also, could you comment on the use of phosphate either as sodium cellulose phosphate or orthophosphate in the treatment of hypercalciuria?

DR. F. P. MULDOWNEY: Inhibitors of urinary stone formation may act either at the point of crys-

tal formation or subsequently to prevent aggregation of these crystals. The subject has been discussed recently and placed in perspective by Fleish [28], who has emphasized the in vitro character of the evidence, and the important methodologic problems, not the least being the difficulty of repeating with whole urine the data previously derived from dilute solutions. The topic remains a theoretical one, as yet difficult to transfer from bench research to clinical evaluation or application. The simple fact remains that supersaturation of the urine is determined in the main by calcium concentration and secondarily by oxalate concentration [28].

Since urinary pyrophosphate is regarded as an inhibitor of stone formation, and since oral ingestion of orthophosphate increases its excretion, this mode of therapy has been employed by a number of workers with varying interpretations [28]. Opinions also vary concerning the important hazard of developing extraskeletal calcification [29, 30].

DR. J. T. HARRINGTON: Dr. Muldowney, what are your thoughts on the importance of dietary manipulation in the treatment of idiopathic hypercalciuria?

DR. F. P. MULDOWNEY: Dietary restriction of calcium is indicated in idiopathic hypercalciuria because urinary calcium may be reduced to values found in control patients when dietary calcium is restricted to 400 to 500 mg/day [31]. In practice, this is readily achieved by avoiding dairy products such as milk and cheese. The possible importance of sodium intake remains to be fully assessed, but recently we have studied the effect of changing sodium intake from 60 to 200 mEq in two consecutive 3-day periods. On this regimen, six stone-forming patients with previous inconstant hypercalciuria with a random diet showed 24-hour urinary calcium excretion to be in the range of 100 to 280 mg with an intake of 60 mEq of sodium per day; this increased to 260 to 550 mg with an intake of 200 mEq of sodium per day on the third day. Clearly dietary sodium restriction may prove to be important. Carbohydrate intake has been shown to affect urinary calcium in acute studies by Lemann, Peiring, and Lennon [32], but more study is needed before carbohydrate restriction should be added to the growing number of dietary prohibitions in stone disease.

DR. D. POWELL: Dr. Muldowney, could you comment on the alleged link between medullary sponge kidney and hyperparathyroidism?

DR. F. P. MULDOWNEY: It is difficult to assign importance to an association between two diseases reported to coincide on relatively few occasions [33–35]. If there is a causal relationship, the primary event might be primary hyperparathyroidism leading to nephrocalcinosis and intersitital nephritis with tubular ectasia, or alternatively a renal calcium leak of sufficient severity to induce secondary hyperparathyroidism, ultimately going on to an autonomous or primary form.

DR. JOHN HARRINGTON: What are the indications for surgery in patients with proven but marginal hyperparathyroidism? If such a patient has had only one or two episodes of stone formation, are we justified in recommending surgery? Is there a role for thiazides in this situation?

DR. F. P. MULDOWNEY: The patients with marginal hyperparathyroidism whom I have discussed have had considerable difficulty with recurrent renal colic and stones. In general, for this group of patients, I think it is best to remove the source of the problem surgically, if one is sure of the diagnosis. A strong point against the use of thiazides under these circumstances is that more severe hypercalcemia may result, and this may go unrecognized if the patient escapes medical supervision. If one could rely on adequate follow-up—perhaps three or four times a year—this approach might be acceptable. But, in my experience, such patients tend not to return for follow-up, so I think it is safer to advise surgery. On the other hand, patients with marginal hyperparathyroidism who have not had recurrent stones or renal colic can be managed conservatively—that is, without surgery or thiazides.

Forum commentary

DR. FREDRIC L. COE (*Director, Division of Renal Medicine, Michael Reese Hospital and Medical Center, Chicago*): Naturally, we are delighted that Dr. Muldowney has found elevated fractional excretion of calcium in most cases of idiopathic hypercalciuria. This need not be primary evidence, however, for a renal leak in the sense that intestinal calcium hyperabsorption could be thought of as leading to chronic suppression of PTH secretion. If increased fractional excretion of calcium can be found to correlate with normal or high levels of serum iPTH, then it seems difficult to escape the conclusion that a renal leak must be present.

Although it has not been described in detail, many published case series provide examples of mild hypercalcemia in primary hyperparathyroidism associated with marked hypercalciuria. The patient presented at this Forum appears to be an ex-

ample of this phenomenon. Even though the increase in apparent filtered load is not marked, it is quite possible to have hypercalciuria, despite increased rather than decreased calcium reabsorption. Fractional excretion of calcium is of course the total urine calcium excretion divided by the product of GFR and the ultrafilterable calcium concentration. Since the ultrafilterable calcium concentration in primary hyperparathyroidism is commonly slightly above normal, the value for fractional calcium excretion tends to be lower than the value obtained by merely dividing calcium excretion by GFR. In other words, it is possible to have marked hypercalciuria with minimal hypercalcemia even in the presence of slightly increased renal tubular calcium reabsorption, and the increased calcium reabsorption is perfectly consistent with the known physiological action of parathyroid hormone.

The probelm of serum parathyroid hormone levels in idiopathic hypercalciuria has vexed many of us. The actual prevalence of "high" values has varied markedly with the immunoassay used. Perhaps it is time that other criteria than the presence or absence of high serum iPTH levels be used to define "renal" hypercalciuria. Although a renal leak theory tends to lead to the prediction of secondary hyperparathyroidism, might it not be worthwhile to try to find more direct ways of diagnosing a renal leak and then see what the iPTH levels are in patients who clearly have this abnormality?

As to the point raised by Dr. Muldowney that the patients from my laboratory could have had primary hyperparathyroidism, I have some reservations. The serum calcium concentrations for these patients were included in the original report. Virtually no values exceeded 10 mg/100 ml, and every patient was studied at least in triplicate; most had quadruplicate samples. If we are to presume that the patients we described had primary hyperparathyroidism, then we are back to the old problem of "normocalcemic" primary hyperparathyroidism, something that Dr. Muldowney probably does not endorse and that I find rather unsatisfactory as a concept. Unlike 1,25-dihydroxy vitamin D, PTH certainly does not augment urinary calcium excretion when the serum calcium concentration is below 10 mg/100 ml; it does in fact raise the fractional reabsorption of calcium. For this reason, one would have great difficulty explaining truly normocalcemic hypercalciuria as a consequence of a primary increase in PTH secretion. It is more likely that some immunoassays tend to reflect higher values of serum iPTH in idiopathic hypercalciuria than do others.

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The editors should like to expand the scope of these exercises by encouraging active participation of the journal's readership in *Nephrology Forum*. Questions or comments pertaining to this month's discussion may be submitted to *Nephrology Forum*, Box 212, New England Medical Center Hospital, 171 Harrison Avenue, Boston, Massachusetts 02111. To be eligible for publication correspondence must be received by December 31, 1979.